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# Children Experience Cognitive Decline Despite Reversal of Brain Atrophy One Year After Resolution of Cushing Syndrome

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**Adults with Cushing syndrome frequently develop brain atrophy, memory impairment, and depression, with partial to complete resolution after cure. The effect of excess glucocorticoid exposure on the brain of children has not been systematically studied. Eleven children (six girls, five boys; ages, 8–16 yr) with endogenous Cushing syndrome seen at the National Institutes of Health Clinical Center from 1999–2000 and 10 healthy age- and sex-matched control subjects were studied. Cognitive and psychological evaluations and magnetic resonance imaging of the brain were done before and 1 yr after cure for patients with Cushing syndrome and once for controls. The estimated duration of Cushing syndrome was 4.4 ± 1.2 yr. When compared with control subjects, children with Cushing syndrome had significantly smaller cerebral volumes ($P < 0.001$), larger ventricles ($P = 0.02$), and smaller amygdala ($P = 0.004$). At baseline, there were no significant differences in IQ between the two groups, and no psychopathology was identified. Despite reversal of cerebral atrophy 1 yr after surgical cure (total cerebral volume, 947 ± 94 *vs.* 1050 ± 74 ml, $P < 0.001$; ventricular volume, 21.4 ± 12.5 *vs.* 14.5 ± 11.6 ml, $P < 0.001$), children with Cushing syndrome experienced a significant ($P < 0.05$) decline in Wechsler IQ scores (Full Scale, 112 ± 19 *vs.* 98 ± 14) and a decline in school performance, without any associated psychopathology. The effect of glucocorticoid excess on the brain of children appears to be different from adults. Despite rapid reversibility of cerebral atrophy, children experience a significant decline in cognitive function 1 yr after correction of hypercortisolism. (*J Clin Endocrinol Metab* 90: 2531–2536, 2005)**

THE ASSUMPTION THAT children respond similarly to adults with respect to disease processes, medication efficacy, and side effects is often erroneous (1). Cushing disease and other endogenous causes of excess cortisol secretion are rare in children. Patients with endogenous causes of Cushing syndrome represent a model in which to study the effects of hypercortisolism, although the degree to which the effects of excess endogenous and exogenous glucocorticoids are comparable is unknown. Moreover, many effects may be dose-related. Prolonged exposure to excess glucocorticoid from an endogenous or exogenous source causes growth retardation and obesity in children (2), but mental changes secondary to exposure to excess glucocorticoid have not been systematically studied in pediatric patients. Studies of adult patients with Cushing syndrome have found that, in the majority of patients, prolonged exposure to excess cortisol results in cognitive and memory impairment and significant psychopathology, most commonly, depression (3, 4). Significant recovery of depressive symptoms and improvement in concentration (5–7) and partial reversibility of cerebral atrophy have been observed in adult patients with Cushing syndrome after remission (8, 9).

To assess the effect of hypercortisolism on the developing child brain, we performed clinical, cognitive, psychological, and magnetic resonance brain imaging studies in children with Cushing syndrome at diagnosis and 1 yr after a return to eucortisolism and in age-and sex-matched controls.

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Abbreviations: BASC, Behavioral Assessment System for Children; BMI, body mass index; HPA, hypothalamic-pituitary-adrenal; ICC, intraclass correlation coefficient; MRI, magnetic resonance imaging; SDS, SD score.

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## Subjects and Methods

### *Subjects*

Eleven children (six females, ages 8–16 yr; five males, ages 9–15 yr) with endogenous Cushing syndrome seen at the National Institutes of Health Clinical Center from 1999–2000 and 10 healthy age- and sex-matched control subjects (six females, ages 8–16 yr; four males, ages 9–16 yr) were studied. Children with Cushing syndrome were evaluated before surgery and 1 yr after surgery. Ten children were diagnosed with Cushing disease and underwent transsphenoidal surgery for removal of a pituitary adenoma. Of these 10 patients, two female patients with Cushing disease had prior transsphenoidal surgery without remission and were referred to the National Institutes of Health for a possible second surgery. One child (8-yr-old female) was diagnosed with primary pigmented nodular adrenocortical disease, not associated with Carney complex, and a bilateral adrenalectomy was performed. Magnetic resonance imaging (MRI) of the brain and psychological testing of healthy subjects were obtained from a parallel study of normal brain development using subjects recruited from the community (10). All subjects underwent physical and neurological examinations. Retrospective growth data for the patients with Cushing syndrome was obtained from their pediatricians' medical records. Control subjects with physical,

neurological, and personal or familial psychological abnormalities (one first-degree relative, or more than 20% of second-degree relatives with psychiatric diagnosis) were excluded. Tanner staging of patients with Cushing syndrome was determined by breast development (females) (11) or testicular size (males) (12), and by a self-administered questionnaire in control subjects (13).

The study was approved by the institutional review boards at the National Institute of Child Health and Human Development and the National Institute of Mental Health. Each parent gave written informed consent, and children over the age of 7 yr gave their assent.

### *Cognitive and psychological studies*

All children were evaluated by a neuropsychologist (E.A.W.). Psychological evaluation included the 12 handedness items from the Physical and Neurologic Examination for Subtle Signs (PANESS) inventory (14) and the Behavioral Assessment System for Children (BASC) (15). The Wechsler Intelligence Scale for Children was administered to subjects under 16 yr of age (16). The Wechsler Adult Intelligence Scale (17) was used to evaluate subjects 16 yr of age or older. Evaluation of the patients with Cushing syndrome also included the California Verbal Learning Test-C (18), the reading and math clusters of the Woodcock-Johnson Psychoeducational Battery Revised: Test of Achievement (19), and questions regarding school performance.

### *MRI*

We examined the hippocampus and amygdala, areas of the brain known to be affected by hormones of the hypothalamic-pituitary-adrenal (HPA) axis (20–22). Volumes of the cerebrum, ventricles, and temporal lobes also were evaluated.

All subjects were scanned on the same GE 1.5 Tesla Signa Advance scanner (GE Signa version 5.4, Milwaukee, WI). Axial slices 1.5-mm-thick and coronal slices of 2 mm were acquired using a three-dimensional spoiled gradient recalled echo in the steady state, with standard head positioning, as previously described (23). All persons involved in the process of obtaining brain measurements were blinded to subject characteristics including age, sex, and diagnosis. The volumes of the cerebrum, ventricles, temporal lobe, hippocampus, and amygdala were quantified using techniques previously validated (10, 23). Total cerebral volume was quantified using an automated program that employs a mathematically modeled template brain to calculate volumetric measurements based on MRI signal intensity characteristics. Each axial slice of the brain was edited by experienced raters to remove artifacts. Lateral ventricular volumes were measured in the coronal plane on all slices on which they were visible using an operator-supervised thresholding technique that segmented cerebrospinal fluid from brain tissue. This analysis was carried out using an image analysis program, the NIH Image 1.61 (24).

Measurements of the temporal lobe, amygdala, and hippocampus were done by manually tracing in the coronal plane by a single experienced operator (S.L.M.) who was blind to any subject characteristics. Our measurement of the temporal lobe, hippocampal formation, and amygdala has been previously described (10, 23). Reliabilities for the quantification of each of the structures were established by having two raters (A.C.V. and S.L.M.) initially measure 10 subjects to determine interrater intraclass correlation coefficients (ICCs). After completion of image analysis for the study, 10 previously measured subjects were redone to account for possible drifts in rater assessment and establish intrarater ICCs. Interrater ICCs were 0.98 for the temporal lobe, 0.74 for the amygdala, and 0.70 for the hippocampus; intrarater ICCs were 0.99 for the temporal lobe, 0.96 for the amygdala, and 0.94 for the hippocampus.

### *Statistical analysis*

Height SD score (SDS) and body mass index (BMI) SDS were determined using anthropometric reference data for U.S. children (25). Demographic and clinical measures were compared between Cushing syndrome patients and age- and sex-matched controls using two sample two-sided Student's $t$ test for continuous measures or $\chi^2$ test for nominal measures. The comparison between Cushing syndrome patients at baseline and at 1-yr follow-up was assessed by using the paired two-sided Student's $t$ test. Statistical significance was accepted for $P < 0.05$. All values are the mean ± SD unless otherwise specified.

## Results

### *Clinical findings*

There were no significant differences between children with Cushing syndrome and the healthy control group with respect to age, gender, pubertal stage, percentage right-handedness, and IQ (Table 1). Both children with Cushing syndrome and the control children had average to above-average pro-rated Wechsler Full Scale IQ (Table 1). No significant learning disabilities were identified in either group.

At baseline, children with Cushing syndrome had impaired growth velocity (1.2 ± 0.9 cm/yr), short stature, younger bone age (up to 3.8 yr delayed), and significantly greater BMI (27.5 ± 3.9 *vs.* 21.9 ± 4.4 kg/m$^2$; $P < 0.001$) than the healthy age-matched controls (Table 1). All of the patients with Cushing syndrome had biochemically confirmed hypercortisolism [urinary free cortisol, 198 ± 75 μg/24 h (546 ± 206 nmol/d); normal range, 8–77 μg/24 h (22–212 nmol/d); urinary free cortisol corrected for body surface area, 147 ± 69 μg/m$^2$·24 h (405 ± 190 nmol/m$^2$·d); normal, <68 μg/m$^2$·24 h (<188 nmol/m$^2$·d)] (26) and lacked diurnal variation in plasma cortisol concentrations [morning cortisol, 19.1 ± 9.5 μg/dl (526 ± 262 nmol/liter); midnight cortisol, 18.7 ± 8.8 μg/dl (515 ± 242 nmol/liter)]. The average duration of Cushing syndrome based on onset of decreased growth velocity was 4.4 ± 1.2 yr (range, 1.0 to 4.5 yr). Three patients had secondary hypothyroidism in the immediate postsurgical period and were placed on thyroid hormone replacement therapy. No other pituitary dysfunction was identified.

One year after surgery, all patients with Cushing syndrome showed biochemical evidence of cure with normal urinary free cortisol levels [17.9 ± 14.5 μg/24 h (49 ± 40 nmol/d); corrected for body surface area, 11.8 ± 9.3 μg/m$^2$·24 h (33 ± 26 nmol/ m$^2$·d]. Ten patients had normalization of their HPA axis based on a normal cosyntropin stimulation test [cortisol > 18 μg/dl (496 nmol/liter) 60 min after cosyntropin administration], whereas one patient remained on physiological doses of hydrocortisone. All patients were euthyroid, and two patients remained on thyroid hormone replacement. During the year after surgery, patients with Cushing syndrome also experienced a significant increase in growth velocity (SDS, −3.8 ± 1.1 *vs.* 5.2 ± 4.1; $P < 0.001$) and height (SDS, −1.1 ± 0.9 *vs.* −0.6 ± 0.8; $P = 0.002$) and a decrease in weight (SDS, 1.3 ± 1.6 *vs.* 0.1 ± 1.3; $P < 0.001$)

**TABLE 1.** Baseline characteristics of children with Cushing syndrome and age- and sex-matched healthy controls

| | Cushing patients (n = 11) | Controls (n = 10) | P |
|---|---|---|---|
| Age (yr) | 12.1 ± 3.4 | 12.6 ± 3.2 | 0.75 |
| No. of females (%) | 6 (55) | 6 (60) | 0.81 |
| Height (SDS) | −1.1 ± 0.9 | 0.7 ± 1.1 | <0.001 |
| Weight (SDS) | 1.3 ± 1.6 | 0.1 ± 0.9 | 0.05 |
| BMI (SDS) | 3.2 ± 2.3 | 0.6 ± 1.3 | <0.001 |
| Tanner stage | 3.0 ± 0.9 | 3.0 ± 1.6 | 0.88 |
| Right handed (%) | 9 (82) | 8 (80) | 0.92 |
| Wechsler (Full Scale IQ) | 112 ± 18 | 120 ± 13 | 0.28 |

Plus-minus values are means ± SD.

and BMI (SDS, 3.2 ± 2.2 *vs.* 0.6 ± 1.3; $P < 0.001$), all indicative of resolution of their hypercortisolism. Overall, their physical appearance improved; they became leaner and more age-appropriate (Fig. 1); and puberty progressed in an age-appropriate manner.

*Cognitive and psychological findings*

At baseline, there were no significant differences between the children with Cushing syndrome and the healthy control group with respect to Full Scale, Verbal and Performance IQ; however, scores tended to be lower in the patients with Cushing syndrome (Wechsler IQ, Cushing *vs.* control: Full Scale, 112 ± 18 *vs.* 120 ± 13; Verbal, 108 ± 16 *vs.* 127 ± 8; Performance, 112 ± 19 *vs.* 112 ± 8). One year after surgery and a return to eucortisolism, patients experienced a significant ($P < 0.05$) decrease in IQ (Fig. 2). Similarly, Woodcock-Johnson achievement scores declined, with a statistically significant decline in mathematics only (reading, 115.5 ± 19.0 *vs.* 108.8 ± 15.8, $P = 0.08$; mathematics, 110.9 ± 19.9 *vs.* 99.5 ± 19.2, $P = 0.02$). Overall, scores that were in the high-average range at baseline declined to the average range at 1-yr follow-up evaluation. There were no significant changes in memory measured by the California Verbal Learning Test (57.3 ± 8.1 *vs.* 55.6 ± 13.0; $P = 0.68$). The BASC did not identify any clinically significant psychological disturbance.

All patients with Cushing syndrome were average to above-average students and the majority reported a decline in school performance 1 yr after surgery. At the time of diagnosis, six patients described themselves as "A" students and taking accelerated classes. One year after surgery, five of the six "A" students had become "B" or "C" students, with a decrease in the number of honors classes. Two patients reported no change in school performance, and no patient reported an improvement in school performance. One of the 11 patients reported missing a significant number of school days in the year after surgery, and none of the patients reported a significant change in social activities.

*MRI findings*

When compared with the age-matched control subjects, children with Cushing syndrome had significantly smaller total cerebral volumes ($P < 0.001$), larger ventricles ($P = 0.02$), and smaller amygdala volumes ($P = 0.004$) (Table 2). Hippocampal volumes were smaller in the patients with Cushing syndrome, but differences between the two groups were not significant (Table 2).

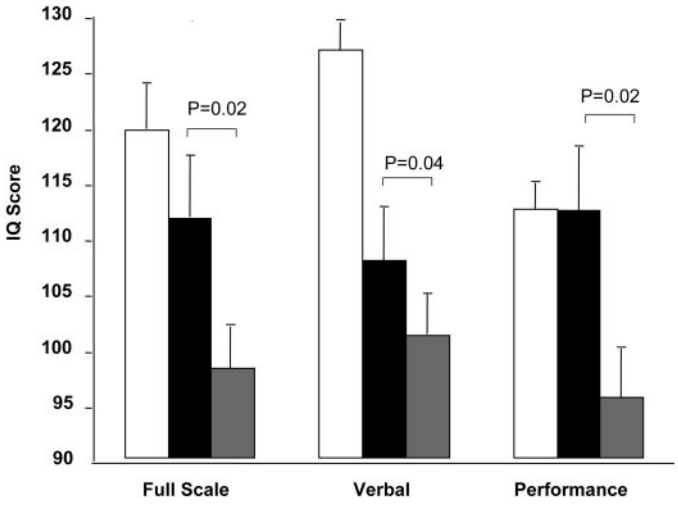


FIG. 2. IQ scores were based on the Wechsler Intelligence Scale (16, 17) for healthy age- and sex-matched control subjects (□), and children with Cushing's syndrome before treatment (■) and 1 yr after surgery and correction of hypercortisolism (▩). The T bars indicate SE values.

A significant ($P < 0.001$) increase in total cerebral volume and decrease in ventricular size was observed 1 yr after surgical cure of Cushing syndrome (Table 2 and Fig. 3). Moreover, the total cerebral volume and ventricular size was comparable to age-matched controls at 1-yr follow-up. Although an increase in the size of the hippocampus was also observed, this increase was not statistically significant. In contrast to other measurements of the brain, no changes over time were observed in the size of the amygdala after correction of hypercortisolism (Table 2).

## Discussion

In this study, we found that children with endogenous Cushing syndrome had average to above-average intelligence despite having significant cerebral atrophy. One year after surgery and a return to eucortisolism, they experienced a significant decline in cognitive function despite almost complete reversal of the cerebral atrophy. This is in contrast to the adult experience. Adults with Cushing syndrome have cognitive and memory impairment and significant psycho-

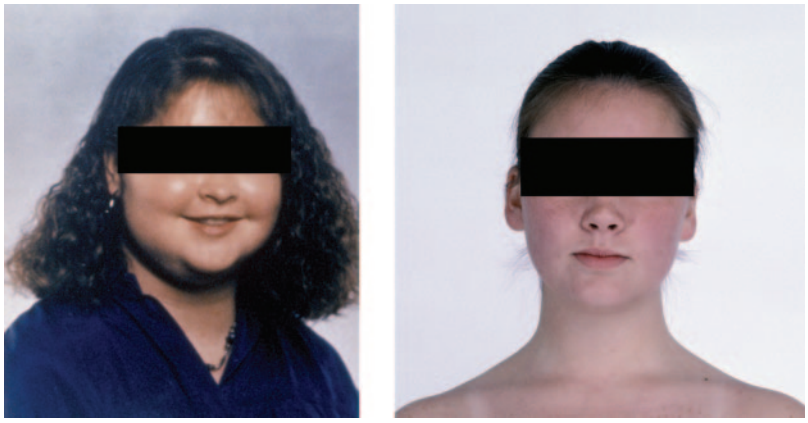

FIG. 1. A 16-yr-old female with Cushing disease (A) experienced weight loss, a pubertal growth spurt, and a decline in school performance 1 yr after surgery and correction of hypercortisolism (B).

**TABLE 2.** Brain volumes of children with Cushing syndrome prior to treatment (baseline), 1 yr after surgical remission and sex- and age-matched healthy controls

| Cerebral volumes (ml) | Control (n = 10) | Cushing baseline (n = 11) | Cushing 1-yr follow-up (n = 11) | P value Cushing baseline *vs.* control | P value Cushing baseline *vs.* 1-yr follow-up |
|---|---|---|---|---|---|
| Total cerebrum | 1119 ± 116 | 947 ± 94 | 1050 ± 74 | <0.001 | <0.001 |
| Lateral ventricle | 10.8 ± 4.2 | 21.4 ± 12.5 | 14.5 ± 11.6 | 0.02 | 0.001 |
| Temporal lobe | 175.1 ± 20.1 | 160.0 ± 20.8 | 171.7 ± 20.1 | 0.11 | <0.001 |
| Hippocampus | 8.2 ± 0.7 | 7.7 ± 0.9 | 8.1 ± 0.8 | 0.19 | 0.08 |
| Amygdala | 7.4 ± 0.8 | 6.1 ± 0.8 | 6.1 ± 0.8 | 0.004 | 0.60 |

Plus-minus values are means ± SD.

pathology during hypercortisolism, with significant recovery of symptoms (5–7) and partial reversal of cerebral atrophy after a return to eucortisolism (8, 9). A decline in cognitive function after cure appears to be unique to the pediatric population.

Children with Cushing syndrome present with symptoms that are somewhat different from those seen in adults (2, 27, 28). The most sensitive indicator of excess glucocorticoid secretion in children is growth retardation, which often precedes other manifestations (28). Other most common clinical characteristics of Cushing syndrome in children are weight gain, obesity, and facial plethora (2), which were present in all of our patients. Biochemical features of Cushing syndrome are similar in pediatric and adult patients (27–29).

Mental changes have not been systematically evaluated in children with Cushing syndrome. However, school performance was reported as satisfactory (2), and children with Cushing syndrome were described to have compulsive behavior with overachievement in school (27, 30). This is in contrast to the poor job performance of adults with Cushing syndrome. These observations are in agreement with our findings of average to above-average IQ scores and excellent school performance in our pediatric patients with Cushing syndrome before treatment. In children, long-term psychological effects of excess glucocorticoid exposure are also unknown.

The depressive symptomatology associated with Cushing syndrome in adults is that of the atypical type (3, 5). Atypical depression is characterized by irritability, hyperphagia, hypersomnia, and increased fatigue, in contrast to melancholic depression which is associated with hyperarousal, hypervigilance, insomnia, and anorexia. None of our pediatric patients had symptoms of depression. In fact, the overachievement previously noted in pediatric patients with Cushing syndrome might be a sign of a paradoxic hyperarousal state with compulsive features. Our psychological evaluation was based on the BASC, a standardized, validated, parent-report which assesses emotional and behavioral problems in children. Although formal psychological interpretation and clinical diagnoses are possible based on the BASC, it is possible that more extensive psychiatric evaluation would have revealed some psychopathology in our children with Cushing syndrome. Undetected depression, or the psychosocial aspects of experiencing a dramatic change in physical appearance, may have been contributing factors.

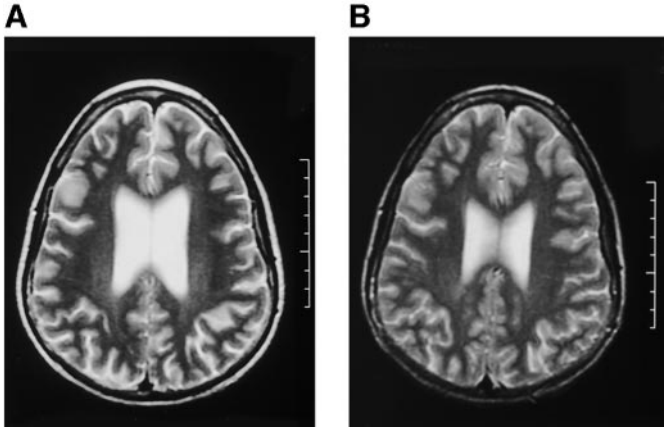


FIG. 3. MRI of the brain of a 15-yr-old male with Cushing disease revealed cerebral atrophy and ventricular enlargement (A) which resolved 1 yr after surgery and correction of hypercortisolism (B).

Autopsy (31, 32) and brain imaging studies have found significant cerebral atrophy in adults with endogenous Cushing syndrome (8, 33). The pathogenesis of this loss of brain volume due to chronic exposure to excess glucocorticoid is unknown. Loss of brain volume may be due to a loss of cell volume, inhibition of the genesis of new neurons or glial cells, the loss of preexisting neurons or glial cells, or some combination of these mechanisms (8, 20). A decrease in brain water volume and ventricular enlargement with resulting tissue compression may also be contributing factors. The occupation of glucocorticoid receptors by supraphysiological doses of glucocorticoid leads to decreased cell excitability and a reversible phase of atrophy of neurons in culture (34, 35). If exposure to excess glucocorticoid persists, neuronal cell death may occur. Glucocorticoids have been shown to increase synaptic accumulation of the excitotoxic glutamate, which may lead to increased susceptibility to cell injury and death (8, 20, 34, 35). Glucocorticoids also inhibit neurogenesis (36) and inhibit glucose utilization by the brain (37). The reversible nature of the cerebral atrophy that characterizes Cushing syndrome suggests that the decrease in brain volume is not merely due to neuronal or glial cell death, and a transient increase in neurogenesis may occur after return to eucortisolism.

Sequential imaging studies have shown a progressive increase in brain volume after correction of hypercortisolism in adult patients with endogenous Cushing syndrome (8). However, after 39 months, brain volume did not reach the expected normal range (8). To the contrary, our patients experienced a rapid increase in brain volume, which reached that of the normal controls within 1 yr after surgical cure. Longitudinal brain imaging data on children has shown developmental changes in some brain structures and an in-

crease in total cerebral volume with increasing age (38). However, significant volumetric changes in 1 yr have not been observed in healthy children (38). The dramatic increase in brain volume observed in our patients with Cushing syndrome is clearly different from previously reported subtle developmental changes and is much greater than the increase in brain volume previously reported in adult patients with Cushing syndrome after cure. Thus, rates of cell recovery and neurogenesis may differ according to age and developmental stage.

Studies of the effect of excess glucocorticoid on the brain have focused mostly on the hippocampus, the brain structure critical for learning and memory (39). The hippocampus plays also an important role in the fine-tuning of the HPA axis by participating in its glucocorticoid negative feedback regulation. Animal studies (40) and human studies of adult patients with chronic hypercortisolemia (41) have shown that prolonged exposure to glucocorticoid excess results in hippocampal atrophy and memory impairment (42). An association between reduced hippocampal volume and lower scores for learning and memory has been shown in adult patients with Cushing syndrome, and memory impairments observed were specific to verbal learning and delayed verbal recall (41). Appropriate treatment of the underlying Cushing syndrome tends to reverse this cognitive impairment in adults (41, 43). Our children with Cushing syndrome had hippocampal volumes smaller than those of the controls, and Verbal IQ scores were somewhat lower than the normal controls. An increase in the volume of the hippocampus was observed 1 yr after remission, whereas paradoxically Verbal IQ scores declined, and memory scores did not change. This increase in hippocampal volume failed to reach statistical significance, most likely due to limitations in our sample size. Thus, in children, despite normalization of total brain and hippocampal volume with time that corresponded to resolution of hypercortisolism, verbal scores declined whereas memory testing was unchanged. These findings are based on limited evaluation of memory in a small sample size.

The amygdala is the brain structure that plays a central role in the processing of fear (44). Glucocorticoids and CRH are important in the regulation of amygdala function (21, 22, 45, 46). Changes in amygdala function have been implicated in the pathophysiology of anxiety and depressive disorders in both adults (47–49) and children (50). The effect of hypercortisolism on the amygdala has not been systematically studied; however, patients with classic congenital adrenal hyperplasia, who have prenatal glucocorticoid deficiency with possible postnatal iatrogenic glucocorticoid excess, have smaller amygdala volume than healthy age- and sex-matched controls (23). In our children with Cushing syndrome, we observed significantly smaller amygdala volumes than those of healthy controls. Unlike the hippocampus, no correction in the size of the amygdala was observed 1 yr after cure.

Several secondary hormonal imbalances occur with hypo- and hypercortisolemia. Patients with Cushing disease have markedly decreased cerebrospinal fluid CRH levels (51), and hyposecretion of CRH may play a role in the pathogenesis of the atypical depression characteristic of adult patients with Cushing syndrome (5). Region-specific changes in dopamine activity occur with chronic hypercortisolemia (52, 53). Chronic hypercortisolism also inhibits sympathoadrenal activity (54, 55) and gonadotropin secretion. Removal of the source of excess endogenous or exogenous glucocorticoid and the institution of physiological glucocorticoid replacement typically results in normal functioning of the HPA axis within 6 months to 1 yr. The time course to normalization of other hormonal imbalances is unknown. The mechanism responsible for the observed cognitive decline in our patients is unknown, but the multiple hormonal imbalances characteristic of Cushing syndrome may play a role.

Our findings suggest that chronic glucocorticoid excess followed by normalization of cortisol results in cognitive decline in children, despite reversal of cerebral and hippocampal, but not amygdala, atrophy. This observed cognitive decline may be due to the prior cortisol excess, the removal of cortisol excess, a relative cortisol deficiency after cure of Cushing syndrome, or a combination of these factors. Studies regarding cognitive changes in other populations with abnormal HPA axis function, such as children with primary or secondary adrenal insufficiency or those receiving pharmacological glucocorticoid therapy for immunosuppression or respiratory disease, have not been done. Excess glucocorticoid, from an endogenous or exogenous source, not only significantly impacts the height, weight, and development of children, but also may have long-lasting effects on the brain and cognition. It is possible that additional follow-up of our patients will show positive cognitive changes. However, our findings indicate that differences between adults and children exist in the cognitive effects of excess glucocorticoid. Additional cognitive, psychiatric, and imaging studies in pediatric patients with iatrogenic and/or endogenous Cushing syndrome are needed to elucidate the long-lasting effects of exposure to abnormal levels of glucocorticoid on the developing brains of children.

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## References

1. **Roberts R, Rodriguez W, Murphy D, Crescenzi T** 2003 Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. JAMA 290:905–911
2. **Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler Jr GB, Nieman LK, Chrousos GP** 1994 Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med 331:629–636
3. **Dorn LD, Burgess ES, Dubbert B, Simpson SE, Friedman T, Kling M, Gold PW, Chrousos GP** 1995 Psychopathology in patients with endogenous Cushing's syndrome: 'atypical' or melancholic features. Clin Endocrinol (Oxf) 43:433–442
4. **Sonino N, Fava GA, Raffi AR, Boscaro M, Fallo F** 1998 Clinical correlates of major depression in Cushing's disease. Psychopathology 31:302–306
5. **Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW, Chrousos GP** 1997 The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. J Clin Endocrinol Metab 82:912–919
6. **Kelly WF, Kelly MJ, Faragher B** 1996 A prospective study of psychiatric and psychological aspects of Cushing's syndrome. Clin Endocrinol (Oxf) 45:715–720
7. **Starkman MN, Schteingart DE, Schork MA** 1986 Cushing's syndrome after

treatment: changes in cortisol and ACTH levels, and amelioration of the depressive syndrome. Psychiatry Res 19:177–188
8. **Bourdeau I, Bard C, Noel B, Leclerc I, Cordeau MP, Belair M, Lesage J, Lafontaine L, Lacroix A** 2002 Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 87:1949–1954
9. **Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE** 1999 Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry 46:1595–1602
10. **Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL** 1996 Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex 6:551–560
11. **Marshall WA, Tanner JM** 1969 Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303
12. **Zachmann M** 1974 Evaluation of gonadal function in childhood and adolescence. Helv Paediatr Acta Suppl 34:53–62
13. **Duke PM, Litt IF, Gross RT** 1980 Adolescents' self-assessment of sexual maturation. Pediatrics 66:918–920
14. **Denckla MB** 1985 Revised neurological examination for subtle signs. Psychopharmacol Bull 21:773–800
15. **Reynolds CR, Kamphaus RW** 1992 Behaviour assessment system for children manual. Circle Pines, MN: American Guidance Services
16. **Wechsler D** 1991 Wechsler intelligence scale for children. 3rd ed. San Antonio, TX: Psychological Corp.
17. **Wechsler D** 1997 Wechsler adult intelligence scale. San Antonio, TX: Psychological Corp.
18. **Delis DC, Kramer JH, Kaplan E, Ober BA** 1994 California verbal learning test-children's version. San Antonio, TX: Psychological Corp.
19. **Woodcock RW, Mather N** 1989 Woodcock Johnson tests of achievement. New York: Riverside Publishing
20. **De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M** 1998 Brain corticosteroid receptor balance in health and disease. Endocr Rev 19:269–301
21. **Beaulieu S, Pelletier G, Vaudry H, Barden N** 1989 Influence of the central nucleus of the amygdala on the content of corticotropin-releasing factor in the median eminence. Neuroendocrinology 49:255–261
22. **Charney DS** 2003 Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Scand Suppl 108:38–50
23. **Merke DP, Fields JD, Keil MF, Vaituzis AC, Chrousos GP, Giedd JN** 2003 Children with classic congenital adrenal hyperplasia have decreased amygdala volume: potential prenatal and postnatal hormonal effects. J Clin Endocrinol Metab 88:1760–1765
24. **Rasband W** 1993 Image 1.61, 1.6 ed. Bethesda, MD: National Institutes of Health [public domain]
25. **Najjar MF, Rowland M** 1987 Anthropometric reference data and prevalence of overweight, United States, 1976–80. Vital Health Stat 11:1–73
26. **Gomez M, Malozowski S, Winterer J, Vamvakopoulos NC, Chrousos GP** 1991 Urinary free cortisol values in normal children and adolescents. J Pediatrics 118:256–258
27. **Devoe DJ, Miller WL, Conte FA, Kaplan SL, Grumbach MM, Rosenthal SM, Wilson CB, Gitelman SE** 1997 Long-term outcome in children and adolescents after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 82:3196–3202
28. **Styne DM, Grumbach MM, Kaplan SL, Wilson CB, Conte FA** 1984 Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenomectomy. N Engl J Med 310:889–893
29. **Mampalam TJ, Tyrrell JB, Wilson CB** 1988 Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. Ann Intern Med 109:487–493
30. **Orth DN, Kovacs WJ** 1998 The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams textbook of endocrinology. 9th ed. Philadelphia: W.B. Saunders; 566
31. **Cope O, Raker JW** 1955 Cushing's disease: the surgical experience in the care of 46 cases. N Engl J Med 253:119–127
32. **Soffer LJ, Iannaccone A, Gabrilove JL** 1961 Cushing's syndrome: a study of fifty patients. Am J Med 30:129–145
33. **Simmons NE, Do HM, Lipper MH, Laws Jr ER** 2000 Cerebral atrophy in Cushing's disease. Surg Neurol 53:72–76
34. **McEwen BS, Sapolsky RM** 1995 Stress and cognitive function. Curr Opin Neurobiol 5:205–216
35. **Sapolsky RM** 1994 The physiological relevance of glucocorticoid endangerment of the hippocampus. Ann NY Acad Sci 746:294–304; discussion, 304–307
36. **Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ** 1999 Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 2:260–265
37. **Kadekaro M, Ito M, Gross PM** 1988 Local cerebral glucose utilization is increased in acutely adrenalectomized rats. Neuroendocrinology 47:329–334
38. **Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL** 2002 Development trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288:1740–1748
39. **Zola-Morgan SM, Squire LR** 1990 The primate hippocampal formation: evidence for a time-limited role in memory storage. Science 250:288–290
40. **Sapolsky RM, Uno H, Rebert CS, Finch CE** 1990 Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 10:2897–2902
41. **Starkman MN, Gebarski SS, Berent S, Schteingart DE** 1992 Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol Psychiatry 32:756–765
42. **Starkman MN, Giordani B, Berent S, Schork MA, Schteingart DE** 2001 Elevated cortisol levels in Cushing's disease are associated with cognitive decrements. Psychosom Med 63:985–993
43. **Jameison K, Dinan TG** 2001 Glucocorticoids and cognitive function: from physiology to pathophysiology. Hum Psychopharmacol 16:293–302
44. **LeDoux JE** 2000 Emotion circuits in the brain. Annu Rev Neurosci 23:155–184
45. **Thompson BL, Erickson K, Schulkin J, Rosen JB** 2004 Corticosterone facilitates retention of contextually conditioned fear and increases CRH mRNA expression in the amygdala. Behav Brain Res 149:209–215
46. **Makino S, Schulkin J, Smith MA, Pacak K, Palkovits M, Gold PW** 1995 Regulation of corticotropin-releasing hormone receptor messenger ribonucleic acid in the rat brain and pituitary by glucocorticoids and stress. Endocrinology 136:4517–4525
47. **Manji HK, Drevets WC, Charney DS** 2001 The cellular neurobiology of depression. Nat Med 7:541–547
48. **Sheline YI** 2000 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biol Psychiatry 48:791–800
49. **Sheline YI, Gado MH, Price JL** 1998 Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 9:2023–2028
50. **Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, Axelson D, Whalen PJ, Casey BJ** 2001 Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry 58:1057–1063
51. **Kling MA, Roy A, Doran AR, Calabrese JR, Rubinow DR, Whitfield Jr HJ, May C, Post RM, Chrousos GP, Gold PW** 1991 Cerebrospinal fluid immunoreactive corticotropin-releasing hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. J Clin Endocrinol Metab 72:260–271
52. **Pacak K, Tjurmina O, Palkovits M, Goldstein DS, Koch CA, Hoff T, Chrousos GP** 2002 Chronic hypercortisolemia inhibits dopamine synthesis and turnover in the nucleus accumbens: an in vivo microdialysis study. Neuroendocrinology 76:148–157
53. **Hochberg Z, Pacak K, Chrousos GP** 2003 Endocrine withdrawal syndromes. Endocr Rev 24:523–538
54. **Cameron OG, Starkman MN, Schteingart DE** 1995 The effect of elevated systemic cortisol levels on plasma catecholamines in Cushing's syndrome patients with and without depressed mood. J Psychiatr Res 29:347–360
55. **Golczynska A, Lenders JW, Goldstein DS** 1995 Glucocorticoid-induced sympathoinhibition in humans. Clin Pharmacol Ther 58:90–98

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